REMARKS/ARGUMENTS

With the entry of the amendments, claims 1-10 and 21-30 will be pending. A declaration of Dr. James Shen in support of the following remarks and a supplemental IDS has been included with this amendment.

Double Patenting

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent Application No. 09/961,563.

Applicants respectfully request that the examiner hold this rejection in abeyance until such time as there is an indication of otherwise allowable subject matter. Only at that time will the applicants be able to determine whether an obviousness-type double patenting rejection still applies.

Rejections - 35 U.S.C. § 112, First Paragraph

Claims 1-10

Claims 1-10 have been rejected as allegedly failing to enable one of ordinary skill in the art to make and use the invention commensurate in scope with the claims.

The Examiner summarized the state of the prior art and the predictability in the art and concluded that one of ordinary skill in the art would have to test "all possible combinations of promoter(s), enhancer element(s), and any gene(s) of interest." Applicants respectfully disagree with the Examiner's summary and this conclusion.

The making and using of the claimed invention may be broken into three parts. The first part is construction of the vector construct to be integrated into an animal. The second part is generation of the transgenic animal. The third and final part is whether the transgene actually functions in the transgenic animal. As for the first part, generation of the vector construct requires routine molecular

biology and is clearly enabled. One of skill in the art would have no difficulty in making any of the vectors commensurate in scope with the claims.

The second part is whether it would be possible to introduce the transgene into an animal such that it integrates into the animal's genome. The examiner has cited to the Wall (1996) review article, for indicating the state in the art as of the filing of the present application on December 4, 1998. The review indicates that the efficiency of transgene expression in animals is very low. However, all the data in the review is taken from earlier reviews summarizing earlier results. In fact, the most up to date data cited in table 1 of Wall (1996) is reference number 53, which was published in 1993, five years before the application was filed. Given the rapid advances in transgene technology, five years is a long time.

A more recent review by Wall (2001) presents a different picture. This Wall article and all references referred to in the declaration are contained in the accompanying IDS. The more recent Wall review surveys two decades of transgenic animal research through 2001, including publications from multiple references from the years between 1992 to 1998 (e.g., Gagne, et al., 1995, Kupriyanov, et al., 1998). Thus this reference gives a review of the state of the art in the period relevant to this invention. According to Wall (2001), "Experience has taught us that once microinjection skills are perfected there are only a few parameters one needs to be concerned about to successfully produce transgenic animals...[Production of transgenic animals by pronuclear microinjection]...is a known technology, which is to say there is a reasonable chance of predicting the outcome of experiments."

Furthermore, a low efficiency of transgene integration does not in and of itself indicate that the making of transgenic animals is not enabled. In fact, the transgene efficiencies show that transgenes can be integrated into the genomes of all animals tested. Wall (2001) indicates that the efficiency is ~1 %, i.e., out of one hundred attempts, one transgenic animal is obtained. Thus, all one of skill in the art needs to do is transfect approximately one hundred embryos and they will get approximately one transgenic animal. For livestock, this efficiency is as high as 5 – 10% of offspring born. As MPEP 2164.01 makes clear,"The fact that experimentation is complex does not necessarily make it undue, if the art typically engages in such experiments."

Additionally Wall (2001), states that while the efficiency of transgenics is low, "At present pronuclear microinjection...is the *least complicated, reliable* method available for producing transgenic animals." (emphasis added). As the Declaration of Dr. Shen indicates, generation of transgenic animals was routine in the art as of filing the application. Low efficiency was expected. Thus it was standard practice to generate hundreds of injected oocytes and then screen for offspring that express the transgene. As an additional note, some of the low efficiency as indicated by the Examiner is due to positional effects of the random integration of the transgenes. The claimed invention, the HS-40 element, provides position independent expression and therefore should increase the efficiency of expression of the transgene. See Table 1, Specification. Thus, while complex and time consuming, generation of a transgenic animal was routine in the art and therefore enabled.

The third and final part is whether the transgene once introduced into an animal will function as claimed. Claim 1 comprises the functional description "wherein the transgenic animal expresses a transcript driven by the promoter, the level of expression in at least one cell type of the animal being proportionally dependent on the copy number of the transgene." Thus the utility of this invention and its claimed function is that the enhancer element will lead to the level of expression in at least one cell type of the animal being proportionally dependent on the copy number of the transgene. For the sake of clarity, the applicants stress that the invention does not depend upon the particular utility of the promoter or the transcript expressed from the promoter. Therefore, whether any particular promoter functions as expected, or any given transcript, be it a gene or otherwise, will have a particular function is not part of the claimed function.

Correspondingly, it does not matter that a given promoter may function poorly in some animals and extremely well in other animals. All that matters is whether the transcript expression is proportional to the copy number. Thus for this part of enablement all that matters is whether the enhancer element is likely to lead to position independent expression in the entire range of animals claimed. There is abundant evidence that elements that generate position independent expression are functional across species. The Declaration of Dr. Shen supports this assertion and summarizes a number of papers that show a broad range of cross-species, cross-promoter and cross-gene function

of position independence elements. For instance, avian position independence elements function in mammals, mammalian elements function in insects, and insect elements function in mammals. See Table A in attached Declaration. Given that insects, mammals and birds are widely evolutionarily divergent, it is logical to assume that HS-40 would work in almost any species of animal.

Additionally, the Examiner has not provided any evidence that indicates that the HS-40 enhancer element is not likely to function in multiple species. The papers cited by the Examiner speak to whether or not a given *protein* or a given *promoter* expressed in different animals will function similarly. In contrast, the references in Table A show that position dependent elements, the subject matter of the current invention, function well in multiple species. MPEP 2164.04 indicates that the Examiner "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." Thus, the applicants respectfully request that the Examiner provide some basis to suggest that the HS-40 element as claimed will not function across species, promoters and genes as indicated by the cited literature.

Rejections - 35 U.S.C. § 112, First Paragraph

Claims 11-20

The Examiner has rejected claims 11-20 as allegedly failing to enable one of ordinary skill in the art to make and use the invention commensurate in scope with the claims. The Examiner has asserted that gene therapy applied to a living animal is not enabled due to its experimental nature.

Applicants respectfully disagree with the Examiner's grounds for rejection and the above statements. However, in order to facilitate prosecution in this case applicants have cancelled claims 11-20, without prejudice or disclaimer, and added new claims 21-30 to cover isolated cells and progeny thereof. With the cancellation of the old claim and addition of new claims, the rejection no longer applies.

Furthermore, the new claims do not read on gene therapy. While such cells could be reintroduced into an animal, the claims are to isolated cells and progeny thereof. These are composition claims. To enable compositions claims, all one needs to do is enable a method of

making the cells that is commensurate with the scope of the claimed composition. See MPEP 2164.01(b) How to Make the Claimed Invention. "As long as the specification discloses at least ***one method*** for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112." (citations omitted, emphasis added) In this case, one of skill in the art can use routine methods in the art to generate transgenic cells that are isolated from an animal. For the avoidance of doubt, it is irrelevant that the cells could have been modified *in vivo* by gene therapy methods and then isolated later. That is another method that could be employed to create the claimed compositions, but does not need to be disclosed or enabled.

Claim Objections

Claims 2 and 12 were objected to because the claims recited the limitation "bird, frog, toad, chicken, turkey" in line 3. Since the claims seem to recite individual species and "bird" is a group term to which chicken and turkey belong, the word "bird" has been deleted in claim 2 per the examiner's suggestion. Claim 12 has been deleted.

In light of the amendments and the above remarks, Applicants submit that the claims meet the requirements of 35 U.S.C. § 112, First Paragraph and request that the rejection of the claims be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **514162000120**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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